Adverse consequences of iron deficiency and the importance of its correction

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Col: Vifor – research grants, consultancy, fees for speaking;
     Amgen – research grants, consultancy
Relevant co-morbidities in CHF that require medical attention

- CAD / ischemia
- Hypertension
- Diabetes mellitus
- Depression / other neurological disease
- Renal dysfunction and kidney injury
- Anemia and iron deficiency
- COPD
- Liver & bowel dysfunction
Mechanisms of Anemia in Chronic Heart Failure & Chronic Kidney Failure

**Haemodilution**
- Plasma Volume ↑

**Forward failure**
- Bone marrow dysfunction

**Iron deficiency**
- Fe²⁺ uptake ↓
- Inflammation induced malabsorption
- Chronic bleeding (aspirin)

**Chronic immune activation**
- TNF alpha - production of Epo ↓
- Epo activity in BM ↓

**Drugs**
- ACE-I: Epo synthesis ↓
- Epo activity in BM ↓

**Chronic kidney failure**
- Production of Epo ↓
- Loss in urine ↑
Iron stores: 35-45 mg/kg BW

Iron distribution:
- Blood – Transferrin (3 mg)
- Hemoglobin (bone marrow & erythrocytes, 1800 mg)
- Storage: mainly liver (1000 mg) & RES (600 mg)
- Muscle – Myoglobin (300 mg)

Iron loss: 1-2 mg / 24 h
(every day !)

Iron uptake: 1-2 mg / 24 h
(critical !)

Andrews NC, NEJM 1999
Inflammation, Hepcidin, Ferroportin & the regulation of iron metabolism

Macrophages (including in liver)

Intestine cells (Enterocytes)

Patients with congestive HF: 10-20% with anemia
Cause of anemia: in 20-30% of cases iron deficiency

- 37 anemic patients with severe CHF, NYHA IV, LVEF – 22%
- bone marrow biopsy confirmed iron deficiency (ID) in 27 of 37 pts

Nanas JN et al.; JACC 2006
1. Absolute iron deficiency
(Reduction in iron stores)
- Causes: chronic blood loss (aspirin), malnutrition, malabsorption
- Diagnosis: low serum ferritin level <30 μg/L

2. Functional iron deficiency
(Disturbed iron metabolism in bone marrow; iron stores =/↓)
- Causes: chronic inflammation & kidney dysfunction
- Diagnosis: serum ferritin 30–99 μg/L or serum ferritin 100–299 μg/L and TSAT<20%

Functional Iron Deficiency = poor Prognosis

definition: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%

Prevalence of ID in CHF patients

Endpoint:
Death & HF hospitalisation

ID (n=64)
Non-ID (n=103)

Jankowska et al., EHJ 2010
Grzeslo A et al. (abstract at HFA 2006)
Iron deficiency but not anaemia is associated with reduced exercise capacity in CHF patients

- Iron deficiency = serum ferritin <100µg/L, or serum ferritin 100–300µg/L with TSAT <20%
- Anaemia = haemoglobin level <12g/dL in women and <13g/dL in men

Jankowska et al. J Cardiac Fail 2011
Iron deficiency but not anaemia is associated with reduced QoL in CHF patients

- HRQoL test: Minnesota Living with Heart Failure Questionnaire (MLHFQ)
- Results adjusted for anaemia, ID and other covariates

Comin-Colet et al. Eur J Heart Fail 2013
Iron deficiency is a bigger problem than anemia

- 157 consecutively eligible patients with CHF
- 2-fold greater risk for mortality in iron-deficient non-anemic patients vs. iron-replete anemic subjects
- 3-fold escalated risk for death irrespective of anaemic status

Okonko et al. JACC 2011
Iron deficiency & anaemia – not 1, but 2 problems

Mortality increases when ID is present

ID is a negative prognostic factor stronger than anemia

Anemia & iron deficiency & exercise capacity

Iron deficiency

\[ \downarrow \text{Hb} \]

(i.e. anemia)

Mitochondrion

Oxidative phosphorylation

\[ \downarrow \text{O}_2 \] \[ \downarrow \text{ATP} \]

\[ \downarrow \text{pVO}_2 = \text{low exercise capacity} \]


Figure adapted from: Anker et al. EJHF 2009
Iron is an essential element for cellular functions\textsuperscript{1–3}

<table>
<thead>
<tr>
<th>Function</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen transport and storage</td>
<td>Haemoglobin, myoglobin</td>
</tr>
<tr>
<td>Mitochondrial electron transport</td>
<td>Respiratory complex I-III</td>
</tr>
<tr>
<td></td>
<td>Cyt-c, Cyt-c oxidase</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Mitochondrial aconitase, lipoate synthase, tyrosine hydroxylase, thyroid peroxidase</td>
</tr>
<tr>
<td>Nucleic acid processing</td>
<td>Phosphoribosyl-pyrophosphate-amidotransferase</td>
</tr>
<tr>
<td>DNA replication</td>
<td>DNA primase</td>
</tr>
<tr>
<td>Cell signalling</td>
<td>Guanylate cyclase</td>
</tr>
<tr>
<td>Antioxidative activity</td>
<td>Myeloperoxidase, catalase, peroxidases, NO synthase</td>
</tr>
</tbody>
</table>

Cyt, cytochrome; NO, nitric oxide

Iron is essential for growth and survival

Iron is particularly important for cells of high mitogenic potential and high energy demand (e.g. skeletal myocytes and cardiomyocytes)

Cairo et al. Genes Nutr 2006
Treatment of CRS, anemia & iron deficiency
– Options –

• Blood transfusion (in severe anemia, if Hgb <9 d/dL, rare in CHF)

• EPO in combination with iv iron or with Vitamin B12 / folic acid
  – Mancini DM et al., Circulation 2003

• ESAs alone (in some cases also with [mostly oral] iron)
  – Amgen Study Programme (Phase 3: RED-HF)

• Iron (oral or iv)
  – 3 PoC / Phase 2 studies have been reported
  – Phase 3: FAIR-HF
Inclusion criteria:
- NYHA II-IV (in NYHA II also CV hosp in last 12 months)
- LVEF ≤ 40%; CHF for ≥ 3 months
- Hb 9-12 g/dL
- TSAT ≥15%

RED-HF
Main results

Haemoglobin

Primary endpoint
Death from any cause or first hospitalization for worsening HF

(P = 0.87 by stratified log-rank test)

(HR = 1.04; 95%CI)

- ESA leads to correction of anaemia
- ESA does not lead to improvements in survival or QoL
- ESA shows somewhat increased risk for thromboembolic adverse events
- Cancer-related adverse events similar in both groups

ESA = Erythropoeisis stimulating agent

RED-HF and the iron status

- Exclusion criterion: TSAT <15%, no ferritin assessed
- Baseline: median TSAT: 24% (19-31)  
  median ferritin: 102 µg/L (53-194)
- When TSAT <20%, iron supplementation was considered, no ferritin cut-off value:
  - i.v. iron: 4.9% (D) vs 5.6% (P), p=0.47
  - p.o. iron: 72.3% (D) vs 73.5% (P), p=0.52

→~50% were iron deficient at time of randomization according to the current definition (ESC HF GLs 2012)
→Predominant treatment with oral iron

The structure of intravenous iron

- Dextran can cause anaphylactic reactions
- Larger/heavier iron–carbohydrate complexes are more stable than smaller/lighter complexes

i.v. Iron Sucrose Improves Kidney Function in Patients with CHF and Iron Deficiency

Inclusion criteria:

- Treatment:
  - 200 mg i.v. iron sucrose per week
  - Weekly for 5 weeks then monthly
  - Duration: 6 months

Hospitalizations:
- i.v. iron: 0/20
- Control: 5/20*

*P<0.01

FAIR-HF Trial -- Study Design

- **Main inclusion criteria:**
  - NYHA class II / III, LVEF ≤40% (NYHA II) or ≤45% (NYHA III)
  - Hb: 9.5–13.5g/dL
  - Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%

- **Treatment adjustment algorithm:**
  - Interruption: Hb>16.0g/dL or ferritin>800µg/L or ferritin>500µg/L, if TSAT>50%
  - Restart: Hb <16.0g/dL and serum ferritin <400µg/L and TSAT<45%

- **Blinding:**
  - Clinical staff: unblinded and blinded personnel
  - Patients: usage of curtains and black syringes for injections

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Anker et al, Eur J Heart Failure 2009;11:1084-1091
75 centers from 11 countries

- Italy: 11 patients
- Spain: 22 patients
- Russia: 200 patients
- Romania: 16 patients
- Ukraine: 103 patients
- Greece: 17 patients
- Germany: 11 patients
- Poland: 60 patients
- France: 11 patients
- Norway: 2 patients
- Argentina: 6 patients
- Czech Republic: 17 patients
- Portugal: 11 patients
- China: 200 patients
# Patient Details

<table>
<thead>
<tr>
<th></th>
<th>FCM (N=304)</th>
<th>Placebo (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td><strong>Gender (% female)</strong></td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td><strong>NYHA class III, n (%)</strong></td>
<td>251 (82.6)</td>
<td>126 (81.3)</td>
</tr>
<tr>
<td><strong>6-min walk test distance (m)</strong></td>
<td>274 ± 105</td>
<td>269 ± 109</td>
</tr>
<tr>
<td><strong>Ischemic etiology (%)</strong></td>
<td>81</td>
<td>79</td>
</tr>
<tr>
<td><strong>Estimated GFR (mL/min/1.73m^2)</strong></td>
<td>64 ± 21</td>
<td>65 ± 25</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td><strong>Hb (g/L)</strong></td>
<td>119 ± 13</td>
<td>119 ± 14</td>
</tr>
<tr>
<td><strong>Serum ferritin (g/L)</strong></td>
<td>53 ± 55</td>
<td>60 ± 67</td>
</tr>
<tr>
<td><strong>ACEi/ARB (%)</strong></td>
<td>92</td>
<td>91</td>
</tr>
<tr>
<td><strong>Beta-Blocker (%)</strong></td>
<td>86</td>
<td>83</td>
</tr>
<tr>
<td><strong>Diuretics (%)</strong></td>
<td>92</td>
<td>90</td>
</tr>
</tbody>
</table>
NYHA, PGA, QoL, 6min-Walking-Test
-- Week 4, 12 & 24 --

**Patient Global Assessment**

- **NYHA functional class**

![Graphs showing changes in NYHA functional class over time](image)

- **Primary endpoints**

**6-minute walk test**

- **KCCQ overall score**

![Graphs showing changes in 6-minute walk test and KCCQ overall score over time](image)

- **EQ-5D VAS score**

![Graphs showing changes in EQ-5D VAS score over time](image)

Anker et al, NEJM 2009;361:2436-2448
NYHA, PGA, QoL, 6min-Walking-Test
-- Week 4, 12 & 24 --

Patient Global Assessment

NYHA functional class

6-minute walk test

KCCQ overall score

EQ-5D VAS score

Anker et al, NEJM 2009;361:2436-2448
Secondary Endpoints:
PGA & NYHA in pre-defined subgroups

<table>
<thead>
<tr>
<th>Metric</th>
<th>Self-reported PGA score</th>
<th>NYHA functional class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients FCM/Placebo</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 120</td>
<td>146/74</td>
<td>0.98</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>146/75</td>
<td></td>
</tr>
<tr>
<td>Median ferritin (µg/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 39</td>
<td>153/72</td>
<td>0.45</td>
</tr>
<tr>
<td>&gt; 39</td>
<td>139/77</td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>119/67</td>
<td>0.22</td>
</tr>
<tr>
<td>≥ 60</td>
<td>173/82</td>
<td></td>
</tr>
<tr>
<td>Median age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 69.7</td>
<td>149/75</td>
<td>0.10</td>
</tr>
<tr>
<td>&gt; 69.7</td>
<td>143/74</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>140/68</td>
<td>0.99</td>
</tr>
<tr>
<td>Female</td>
<td>152/81</td>
<td></td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>52/27</td>
<td>0.66</td>
</tr>
<tr>
<td>Class III</td>
<td>240/122</td>
<td></td>
</tr>
<tr>
<td>Median ejection fraction (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 33</td>
<td>169/70</td>
<td>0.86</td>
</tr>
<tr>
<td>&gt; 33</td>
<td>123/79</td>
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<tr>
<td>CHF</td>
<td></td>
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<tr>
<td>Non-Ischemic</td>
<td>56/30</td>
<td>0.60</td>
</tr>
<tr>
<td>Ischemic</td>
<td>236/119</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>202/113</td>
<td>0.87</td>
</tr>
<tr>
<td>Yes</td>
<td>90/36</td>
<td></td>
</tr>
<tr>
<td>Median BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 27.37</td>
<td>150/71</td>
<td>0.94</td>
</tr>
<tr>
<td>&gt; 27.37</td>
<td>142/78</td>
<td></td>
</tr>
</tbody>
</table>
iv-FCM improves PGA & NYHA class in CHF patients with and without anemia

**Self-Reported Patient Global Assessment**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Ferric Carboxymaltose</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td>≤120 (g/liter)</td>
<td>146</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;120 (g/liter)</td>
<td>146</td>
<td>75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NYHA Functional Class**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Ferric Carboxymaltose</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>≤120 (g/liter)</td>
<td>148</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;120 (g/liter)</td>
<td>146</td>
<td>76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**week 24 results**

**Patients with anaemia (at BL)**

<table>
<thead>
<tr>
<th></th>
<th>FCM</th>
<th>Placebo</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin (μg/L)</td>
<td>275±18</td>
<td>68±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>29±1</td>
<td>17±1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>127±1</td>
<td>118±2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Patients without anaemia (at BL)**

<table>
<thead>
<tr>
<th></th>
<th>FCM</th>
<th>Placebo</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin (μg/L)</td>
<td>349±19</td>
<td>80±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>30±1</td>
<td>22±1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>133±1</td>
<td>132±1</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*Mean treatment effect, adjusted for the baseline value

Anker et al, NEJM 2009;361:2436-2448
Anemia & iron deficiency & organ performance

Iron deficiency

↓ Hb
(i.e. anemia)

Mitochondrion

↓ O₂ delivery

↓ O₂ utilization

↓ organ performance

O₂ delivery

O₂ utilization

Effect of iv-iron on kidney function

Change in eGFR from baseline (mL/min.1.73m²):*

Treatment effect
(mL/min/1.73m²):* 2.8 ± 1.5  3.0 ± 1.5  4.0 ± 1.7

* LSM mean ± SE

Ponikowski et al. 2014 (submitted)
### Treatment effect on renal function in pre-specified subgroups

<table>
<thead>
<tr>
<th>Endpoint (Week 24)</th>
<th>FCM</th>
<th>Placebo</th>
<th>Treatment effect mL/min/1.73m²</th>
<th>P_interaction value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m²</td>
<td>8.19 ± 1.42</td>
<td>6.13 ± 2.00</td>
<td>-2.06 ± 2.32</td>
<td>0.72</td>
</tr>
<tr>
<td>eGFR ≥60 mL/min/1.73 m²</td>
<td>-0.24 ± 1.23</td>
<td>-5.31 ± 1.87</td>
<td>5.07 ± 2.25</td>
<td>0.71</td>
</tr>
<tr>
<td>Hb ≤12 g/dL</td>
<td>4.11 ± 1.42</td>
<td>1.10 ± 2.04</td>
<td>-3.01 ± 2.13</td>
<td>0.71</td>
</tr>
<tr>
<td>Hb &gt;12 g/dL</td>
<td>2.76 ± 1.22</td>
<td>-2.46 ± 1.86</td>
<td>5.22 ± 2.18</td>
<td>0.71</td>
</tr>
<tr>
<td>Ferritin ≤39 ng/mL</td>
<td>4.35 ± 1.30</td>
<td>-1.58 ± 2.02</td>
<td>5.93 ± 2.32</td>
<td>0.65</td>
</tr>
<tr>
<td>Ferritin &gt;39 ng/mL</td>
<td>2.32 ± 1.34</td>
<td>0.36 ± 1.88</td>
<td>-1.96 ± 2.22</td>
<td>0.65</td>
</tr>
<tr>
<td>Age ≤69.7 years</td>
<td>3.22 ± 1.42</td>
<td>-2.64 ± 2.15</td>
<td>5.86 ± 2.31</td>
<td>0.36</td>
</tr>
<tr>
<td>Age &gt;69.7 years</td>
<td>3.61 ± 1.21</td>
<td>1.45 ± 1.75</td>
<td>-2.16 ± 2.22</td>
<td>0.36</td>
</tr>
<tr>
<td>Male</td>
<td>3.29 ± 1.54</td>
<td>2.02 ± 2.40</td>
<td>-1.27 ± 2.18</td>
<td>0.22</td>
</tr>
<tr>
<td>Female</td>
<td>3.46 ± 1.09</td>
<td>-2.41 ± 1.52</td>
<td>5.87 ± 2.32</td>
<td>0.22</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>1.31 ± 1.63</td>
<td>-1.80 ± 2.45</td>
<td>3.11 ± 2.22</td>
<td>0.74</td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>3.88 ± 1.09</td>
<td>-0.20 ± 1.60</td>
<td>4.08 ± 2.32</td>
<td>0.74</td>
</tr>
<tr>
<td>LVEF ≤33%</td>
<td>4.21 ± 1.41</td>
<td>2.45 ± 2.31</td>
<td>-1.76 ± 2.22</td>
<td>0.50</td>
</tr>
<tr>
<td>LVEF &gt;33%</td>
<td>2.44 ± 1.11</td>
<td>-3.40 ± 1.46</td>
<td>5.84 ± 2.32</td>
<td>0.50</td>
</tr>
<tr>
<td>Non-ischaemic HF</td>
<td>5.40 ± 2.73</td>
<td>0.64 ± 3.89</td>
<td>4.76 ± 2.32</td>
<td>0.95</td>
</tr>
<tr>
<td>Ischaemic HF</td>
<td>2.97 ± 0.95</td>
<td>-0.86 ± 1.42</td>
<td>3.83 ± 2.32</td>
<td>0.95</td>
</tr>
<tr>
<td>Non diabetic</td>
<td>3.30 ± 1.07</td>
<td>-1.63 ± 1.50</td>
<td>5.03 ± 2.32</td>
<td>0.67</td>
</tr>
<tr>
<td>Diabetic</td>
<td>3.77 ± 1.88</td>
<td>2.88 ± 3.19</td>
<td>-0.89 ± 2.32</td>
<td>0.67</td>
</tr>
<tr>
<td>BMI ≤27.37kg/m²</td>
<td>3.66 ± 1.25</td>
<td>-1.67 ± 1.90</td>
<td>5.33 ± 2.32</td>
<td>0.55</td>
</tr>
<tr>
<td>BMI &gt;27.37kg/m²</td>
<td>3.08 ± 1.39</td>
<td>0.12 ± 1.98</td>
<td>-2.96 ± 2.32</td>
<td>0.55</td>
</tr>
</tbody>
</table>
Prevalence of Iron Deficiency in CKD

Bone marrow biopsy revealed severe iron deficiency in 46 of 47 CKD patients (Hb <12 g/dl)\(^2\)

NHANES program (1988-2004)\(^1\)

- Percentage with serum ferritin <100 ng/ml or TSAT <20%
- CrCl (ml/min)

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14.99 (n=41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-29.99 (n=202)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-59.99 (n=2579)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NHANES, National Health and Nutrition Examination Survey
CrCl = creatinine clearance; TSAT = transferrin saturation

## Safety Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Patients with events (Incidence per 100-patient years at risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FCM (N=305)</td>
</tr>
<tr>
<td>Death</td>
<td>5 (3.4)</td>
</tr>
<tr>
<td>CV death</td>
<td>4 (2.7)</td>
</tr>
<tr>
<td>Death due to worsening HF</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>First hospitalization</td>
<td>25 (17.7)</td>
</tr>
<tr>
<td>Hospitalization for any CV reason</td>
<td>15 (10.4)</td>
</tr>
<tr>
<td>First hospitalization for worsening HF</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>Any hospitalization or death</td>
<td>30 (21.2)</td>
</tr>
<tr>
<td>Hospitalization for any CV reason or death</td>
<td>20 (13.9)</td>
</tr>
<tr>
<td>First hospitalization for worsening HF or death</td>
<td>11 (7.5)</td>
</tr>
</tbody>
</table>
## Reported Adverse Events

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>FCM (N=305)</th>
<th>Placebo (N=154)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorder</td>
<td>38 (27.6)</td>
<td>33 (50.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>24 (16.9)</td>
<td>5 (6.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>General disorder or administration site condition</td>
<td>23 (16.2)</td>
<td>6 (8.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Injection site pain or discoloration</td>
<td>6 (4.1)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>Infection or infestation</td>
<td>50 (37.0)</td>
<td>24 (35.8)</td>
<td>0.97</td>
</tr>
<tr>
<td>Abnormal laboratory test, vital sign, physical finding</td>
<td>32 (23.0)</td>
<td>10 (14.0)</td>
<td>0.17</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>22 (15.6)</td>
<td>14 (20.3)</td>
<td>0.44</td>
</tr>
<tr>
<td>Respiratory, thoracic or mediastinal disorder</td>
<td>9 (6.2)</td>
<td>10 (14.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Vascular disorder</td>
<td>20 (14.0)</td>
<td>11 (15.7)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

No severe or serious hypersensitive reactions

Adverse events are classified by the Medical Dictionary for Regulatory Activities (MedDRA) and are reported by system organ class when they occurred for more than 4% of patients in total.
The 2012 ESC heart failure guidelines

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: John J. V. McMurray (Chairperson) (UK)*, Stamatis Adamopoulos (Greece), Stefan D. Anker (Germany), Angelo Auricchio (Switzerland), Michael Böhm (Germany), Kenneth Dickstein (Norway), Volkmar Falk (Switzerland), Gerasimos Filippatos (Greece), Cândida Fonseca (Portugal), Miguel Angel Gomez Sanchez (Spain), Tiny Jaarsma (Sweden), Lars Køber (Denmark), Gregory Y. H. Lip (UK), Aldo Pietro Maggioni (Italy), Alexander Parkhomenko (Ukraine), Burkert M. Pieske (Austria), Bogdan A. Popescu (Romania), Per K. Rønnevik (Norway), Frans H. Rutten (The Netherlands), Juerg Schwitter (Switzerland), Petar Seferovic (Serbia), Janina Stepinska (Poland), Pedro T. Trindade (Switzerland), Adriaan A. Voors (The Netherlands), Faiez Zannad (France), Andreas Zeiher (Germany).
New ESC Guidelines HF 2012

Measurement of iron parameters are newly recommended (1C) as standard for the diagnosis in ambulatory patients suspected of having HF:

“In addition to standard biochemical [sodium, potassium, creatinine/estimated glomerular filtration rate (eGFR)] and haematological tests (haemoglobin, haematocrit, ferritin, leucocytes, and platelets), …”

**TSAT** = Serum iron/TIBC x 100  
**TIBC** = Total Iron-Binding Capacity

Iron deficiency may contribute to muscle dysfunction in HF and causes anaemia. In a single RCT, 459 patients with NYHA class II or III systolic HF, a haemoglobin concentration between 9.5 and 13.5 g/dL, and iron deficiency (see below) were randomized 2:1 to i.v. ferric carboxymaltose or saline. In this trial, iron deficiency was diagnosed when serum ferritin was <100 µg/L or when the ferritin concentration was between 100 and 299 µg/L and transferrin saturation was <20%. Over 6 months of treatment, iron therapy improved self-reported patient global assessment and NYHA class (as well as 6-min walk distance and health-related quality of life) and may be considered as a treatment for these patients. The effect of treating iron deficiency in HF-PEF and the long-term safety of iron therapy in HF is unknown.
Limitations of the FAIR-HF study

- The FAIR-HF study:
  - Promising results, but the only double-blind, placebo-controlled clinical trial
    - Results need to be replicated
  - Primary endpoint: NYHA and PGA: optimal decision?
    - Studies need to evaluate different endpoints
      (CONFIRM-HF & EFFECT-HF ongoing -- 1000 mg injections in 1 min)
  - Relatively short study duration (6 months)
    - Studies need longer follow-up (patients exposition), with more safety data
  - Repeated 200mg doses
    - Higher single doses (up to 1000 mg) to be evaluated
Mortality and hospitalization in CHF with i.v. iron sucrose

LVEF < 35%
Anaemia: Hb < 12.5 g/dl (men); Hb < 11.5 g/dl (women)
ID: Ferritin < 100 ng/mL or TSAT < 20%

Treatment:
- i.v. iron group: 200mg/wk for 5wks, after 6 mt 200mg if Hb < 11.0 g/dl and/or TSAT < 20%
- No oral iron and/or ESA given in both groups

CHF – Consolidating the Evidence

Meta-analysis III (all CHF)
FAIR-HFpEF

Meta-analysis II (syst CHF)
iCHF
EFFECT-HF

CONFIRM-HF
FAIR-HF

Symptom, QoL, Function

Mortality

Meta-analysis II (syst CHF)
Meta-analysis III (CHF)
age/gender adjusted OR for serum iron to predict stroke: 0.96 (0.92–1.00), p=0.036
iv iron therapy reduces platelet numbers

Von Haehling S. et al.
Abstract (Poster) ASN 2012
Iron Therapy is Under-Utilized in ND-CKD

European Best Practice Guidelines state:

“All CKD patients with renal anemia undergoing treatment with an erythropoiesis stimulating agent (ESA) should be given supplementary iron ...regardless of dialysis status”¹

... but 33% of patients with non-dialysis CKD are NOT given iron therapy when starting ESA therapy

- Data from 1,060 patients with ND-CKD receiving ESA therapy²

Retrospective data from 1,997 patients starting dialysis 1999-2000 at 779 centers.
ESA = erythropoiesis stimulating agent

• **Design:** Multicentre, randomized (1:1), double-blind, placebo-controlled

• **Main inclusion criteria:**
  – NYHA class II / III, LVEF ≤40%
  – Iron deficiency: serum ferritin <100 µg/L or 100-300 µg/L, if TSAT <20%
  – Hb: 9.5–13.5g/dL

• **Primary endpoint**
  ✓ Change in LVEF determined by cardiac MRI at week 12
  ✓ Change in GFR determined by radionuclide Chromium-51-EDTA at week 12

• **Secondary endpoints**
  ✓ Changes in biomarkers for iron deficiency, renal function, cardiac function, NYHA functional class, PGA and QoL
  ✓ Overall safety over the treatment period

Clinicaltrials.gov identifier: NCT01837082.
FAIR-HFpEF

Design

- **Design**: Multicentre, randomized (1:1), double-blind, placebo-controlled

- **Main inclusion criteria**:
  - NYHA class II / III, LVEF > 45%
  - BNP > 100 pg/mL or NT-proBNP > 300 pg/mL
  - 6MWT < 450m
  - Iron deficiency: serum ferritin <100 µg/L or TSAT <20%
  - Hb: 9.5–14.5g/dL

- **Primary endpoint**
  - ✓ Change in 6MWT at week 24

- **Secondary endpoints**
  - ✓ Change in biomarkers for iron deficiency, renal function, cardiac function, NYHA functional class, PGA and QoL
  - ✓ Overall safety over the treatment period
Implications for clinical practice

Anemia in CHF patients:
- Sign of poor morbidity and mortality
- Increased Hgb: QoL, symptoms, ex.capacity not improved
- Treatment with ESAs: RED-HF trial (for M&M) neutral

Iron deficiency in CHF patients (with CKD):
- New significant therapeutic target (in patients ± anemia)
- Can easily be detected using ferritin & TSAT:  
  a) ferritin<100, b) ferritin <300 & TSAT <20%
- ESC/HFA HF GL 2012: iv FCM “may be considered as a treatment for these patients”

McMurray JJ et al, EHJ & EJHF 2012
Problems & solution in iron therapy

- Iron overload
  - checking for ferritin & %TSAT after iron application

- Hypersensitivity & iron
  - inclusion / exclusion criteria
  - in reality, not observed in CHF trials

- Infections & iron
  - inclusion / exclusion criteria (CrP>10 excluded)
  - in reality, not observed in CHF trials